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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ZEMAN, ROBERT A	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 06/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/913,772	RENNO ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44,45,47-49,51-60 and 62-86* is/are pending in the application.

4a) Of the above claim(s) *58,59 and 67-86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44,45,47-49,51-57,60 and 62-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3/31/06.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed on 3-31-2006 are acknowledged. Claims 44-45, 47-49, 51-53, 55, 57, 60 and 66-67 have been amended. Claims 46, 50 and 61 have been cancelled. Claims 44-45, 47-49, 51-60 and 62-86 are pending. Claims 58-59 and 67-86 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Claims 44-45, 47-49, 51-57, 60 and 62-66 are currently under examination.

Information Disclosure Statement

The Information Disclosure Statement filed on 3-31-2006 has been considered. An initialed copy is attached hereto.

Claim Objections Withdrawn

The objection to claim 66 for reciting material drawn to non-elected inventions is withdrawn in light of the amendment thereto.

Claim Rejections Withdrawn

The rejection of claims 44-46, 48-52 under 35 U.S.C. 102(b) as being anticipated by Rauly et al. (Research in Immunology, Vol 149 No. 1, page 99, Jan 1998) is withdrawn in light of the amendment to claim 44. The cited art does not disclose an OmpA protein comprising the sequence of SEQ ID NO:2.

The rejection of claims 44-55, 57, 60-61 and 65 are rejected under 35 U.S.C. 102(e) as being anticipated by Binz et al. (U.S. Patent 6,197,929) is withdrawn in light of the amendment to claim 44. The cited art does not disclose an OmpA protein comprising the sequence of SEQ ID NO:2.

Claim Rejections Maintained and New Grounds of Rejection

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-45, 47-49, 51-57, 60 and 62-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons set forth in the previous Office action in the rejection of 44, 46-50 and 60-66. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues:

1. An enterobacterium OmpA protein comprising the sequence of SEQ ID NO:2 is described with particularity and therefore provides the necessary description.

Applicant's arguments have been fully considered and deemed non-persuasive.

The rejected claims, as amended, are drawn to the use of pharmaceutical compositions comprising the enterobacterium (*Klebsiella pneumoniae*) OmpA protein comprising the

sequence of SEQ ID NO:2 capable of generating or enhancing a cytotoxic T cell response an immune response in an animal (including man) ***to*** a tumor cell. This directed immune response is conveyed by the antigen not the OmpA protein that serves as an antigen. Consequently, in order to properly describe the claimed invention, the antigens must be satisfactorily described.

As outlined previously, to fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. To adequately describe the genus of *pharmaceutical* compositions comprising the enterobacterium (*Klebsiella pneumoniae*) OmpA protein and a tumor antigen, Applicant must adequately describe the antigenic determinants (immunoepitopes) that elicit an cytotoxic T cell response directed against a given tumor cell not just those determinants that would elicit an immune response to the OmpA protein or the antigen since the antigen OmpA protein can be immunogenic but not induce an cytotoxic T cell response directed against a tumor cell

The specification, however, does not disclose distinguishing and identifying features of a representative number of members of the genus of pharmaceutical compositions to which the claims are drawn, such as a correlation between the structure of the surface marker and its recited function (to elicit an cytotoxic T cell response directed against a tumor cell), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the

claimed genus of immunogenic compositions. Moreover, the specification fails to disclose which amino acid residues (if any) are essential to the function of the immunoepitope (antigen) or which amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of immunoepitopes to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus of pharmaceutical compositions capable of stimulating a cytotoxic T cell response in an animal against a tumor cell.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112,

paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan et al. (*Nature Biotechnology* 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is

necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a directed immune response to a given pathogen can only be identified empirically. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of immunoepitopes, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of pharmaceutical compositions capable of stimulating a cytotoxic T cell response in an animal *to* a tumor cell (as opposed to the OmpA protein). Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of the immunoepitopes (antigenic determinants) is not deemed representative of the genus of pharmaceutical compositions to which the claims refer.

Claims 44-45, 47-49, 51-57, 60 and 62-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth in the previous Office action in the rejection of claims 44, 46-50 and 60-66. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant argues:

1. The claims have been amended to read on methods for generating or increasing a cytotoxic T cell response against a tumor cell utilizing a pharmaceutical composition comprising an OmpA protein having the sequence set forth in SEQ ID NO:2.

2. The specification discloses methods of administration of the claimed composition and discloses methods for analysis of the claimed response.

3. With regard to claims 60-64, enablement for the treatment or prevention of cancer in an animal, including an immunocompetent animal may be found in Example 5.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Point 1, the rejected claims, as amended, are drawn to the use of pharmaceutical compositions comprising the enterobacterium (*Klebsiella pneumoniae*) OmpA protein comprising the sequence of SEQ ID NO:2 capable of generating or enhancing a cytotoxic T cell response an immune response in an animal (including man) ***to*** a tumor cell. This directed immune response is conveyed by the antigen not the OmpA protein that serves as an antigen.

With regard to Point 2, the inability to predict whether a given antigen would induce a directed immune response against a given tumor cell demonstrates the unpredictable nature of the claimed invention (see below). Hence, the specification is not enabling for the full scope of the claimed invention.

With regard to Point 3, contrary to Applicant's assertion, Example 5 (or any other part of the specification) does not provide support for the prevention of cancers of any type in **any** animal. To date, there is no "cancer vaccine" known in the art.

As outlined previously, the rejected claims are drawn to pharmaceutical compositions

comprising the enterobacterium (*Klebsiella pneumoniae*) OmpA protein (comprising SEQ ID NO:2) capable of generating or enhancing a cytotoxic T cell response an immune response in an animal (including man) *to* a tumor cell. However, Applicant has failed to demonstrate that said enterobacterium (*Klebsiella pneumoniae*) OmpA protein is capable of generating or enhancing the claimed immune response (a cytotoxic T cell response an immune response in an animal (including man) *to* any tumor cell). While the skill in the art of immunology is high, to date, prediction of a specific immune response for any given composition in any given animal is quite unpredictable. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome **and form immunoepitopes**. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, as evidenced by Greenspan et al. (*Nature Biotechnology* **7**: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the

molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a directed (protective) immune response to a given pathogen **can only be identified empirically**. This constitutes undue experimentation. Therefore, given the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of a directed immune response, the specification, as filed, does not provide enablement for pharmaceutical compositions comprising the enterobacterium (*Klebsiella pneumoniae*) OmpA protein (comprising SEQ ID NO:2) capable of generating or enhancing a cytotoxic T cell response an immune response in an animal (including man) *to* a tumor cell.

The rejection of claims 60-64 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods utilizing peptides comprising SEQ ID NO:4 and recombinant P40 (OmpA) to reduce the viability of tumor cell based xenographs in immunodeficient mice, does not reasonably provide enablement for the utilization of OmpA/"antigen" combination to treat or prevent cancer in an immunocompetent animal is maintained for reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Additionally, the specification is not enabling for the

use of OmpA for the treatment or prevention of infectious agents (i.e. viruses, bacteria etc),

Applicant argues:

1. Applicant relies on the skill of those in the art of tumor immunotherapy to evaluate immunotherapeutic technologies for the treatment or prevention of cancer.

2. It is well settled that the USPTO is not the FDA and may not require clinical testing to substantiate that which is known in the art.

3. Thurner et al. exemplifies the understanding of those skilled in the art at the time of the invention with regard to tumor immunotherapy for the treatment or prevention of cancer in human patients.

4. Thurner et al. disclose that it has been established that CTLs can recognize tumor antigens and kill tumors.

5. Thurner et al. demonstrate tumor regressions and attribute the tumor regression to the induction of tumor-specific CTLs. Hence, those skilled in the art would readily accept that the instant *in vivo* models correlate with established methodology for treating or preventing human tumors through immunotherapy techniques which endeavor to increase cytotoxic T cells responses.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Points 1 and 3-5, Thurner et al. does not exemplify the art. Moreover, it should be noted that Thurner et al. only deals with treatment of cancers, not the prevention of cancers. Moreover, on the basis of experimentation performed using an animal model, the specification asserts the invention can be used to treat or prevent cancer. The problem with

accepting such an assertion lies in the fact that the data generated using such mouse models cannot be reasonably extrapolated to reliably and accurately predict whether the claimed invention can be used to attenuate at least a substantial number of pathoangiogenic conditions comprising cancer and furthermore, as of yet, the clinical, therapeutic application of cancer "vaccines" to attenuate cancer has been met with very little success. In addition to references cited in preceding Office action, which also describe such disappointing results and attribute the lack of success to various differences, such as the poor extrapolation of promising preclinical data to predict clinical efficacy, Wang et al. (*Exp. Opin. Biol. Ther.* 2001; 1 (2): 277-290) reviews the state of the art of T-cell-directed cancer vaccines for treatment of melanoma and states:

> Saved for scattered reports, however, the success of these approaches has been limited and T-cell-directed vaccination against cancer remains at a paradoxical standstill whereby anticancer immunization can be induced but is not sufficient, in most cases, to induce tumour regression (abstract).

Wang et al. further states:

> Among the questions raised by this paradoxical observation [that systemic T-cell responses to vaccines often do not lead to objective clinical tumor regression] stands the enigma of whether tumour resistance to immunotherapy is due to insufficient immune response or because tumour cells rapidly adapt to immune pressure by switching into less immunogenic phenotypes [citations omitted].

In addition, Kelland (*Eur. J. Cancer.* 2004 Apr; **40** (6): 827-836) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). While the successful use of such models in cytotoxic drug development is conclusive, Kelland discloses that today there is far less focus on the development of such drugs (page 833, column 2); rather, the focus is upon the development of "molecularly-targeted", largely cytostatic drugs,

such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the models are of limited value, because such mechanisms depend upon the recruitment of the host's (i.e., mouse) immune response, which differs from or is not reflective of that found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need to be justified on a case-by-case basis (page 835, column 1). Still, Kelland et al. does not altogether discount the usefulness of such models, since, at present, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even in silico methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2). Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not.

Moreover, as noted in preceding Office action, Gura (of record) teaches that although researchers had hoped that xenografts would prove to better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, "the results of xenograft screening turned out to be not much better than those obtained with the original models". Gura states that as a result of their efforts, " '[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs' ".

With further regard to the predictive value of various different preclinical models,

Voskoglou-Nomikos et al. (*Clin. Cancer Res.* 2003 Sep 15; 9: 4227-4239) reports in a retrospective analysis that mouse allograft models were not predictive and xenograft models were only predictive for non-small cell lung and ovarian cancers, but not for breast or colon cancers; see entire document (e.g., the abstract).

Finally, Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Applicant has argued that the use of xenografts in mice for evaluating therapeutic efficacy of compositions for treating humans is well established; agreeably the model has been utilized, but its use should not be considered sufficient to show that the claimed invention can be used without undue or unreasonable experimentation because of the poor extrapolation of the results to accurately and reliably predict the effectiveness of treating humans with the same agent or regimen. Schuh (*Toxicologic Pathology*. 2004; **32** (Suppl. 1): 53-66) reviews the trials, tribulations and trends in tumor modeling in mice to disclose, for example, that "[c]ommon reliance on survival and tumor burden data in a single mouse model often skews expectations towards high remission and cure results; a finding seldom duplicated in clinical trials" (abstract).

Furthermore, Schuh discloses, "[d]espite historical significance and ongoing utility, tumor models in mice used for preclinical therapeutic intervention often error towards false positive results and curing cancer in mice" (page 62, column 1). Given the noted limitations of xenograft models, Schuh suggests that testing in tumor-bearing animals may help to improve the predictive value of animal modeling; see entire document (e.g., the abstract).

Bibby (*Eur. J. Cancer.* 2004 Apr; **40** (6): 852-857) teaches that in the interest of finding more clinically relevant models, orthotopic models have been developed; see entire document (e.g., the abstract). In such "orthotopic" models, treatment is initiated after removal of the primary tumor and distant metastases are well established and macroscopic. These models have their advantages, but the procedures involved in using such models are far more difficult and time-consuming than conventional subcutaneous (e.g., xenograft) models; see, e.g., page 855, column 2.

The position of the Office is further substantiated by the teachings of Peterson et al. (*Eur. J. Cancer.* 2004; **40**: 837-844). Peterson et al. teaches numerous agents have show exciting activity in preclinical models and yet have had minimal activity clinically; see, e.g., the abstract. Such disappointments, Peterson et al. discloses, "have led to reasonable skeptism about the true value of both syngeneic and xenograft rodent tumour models in accurately identifying agents that will have important clinical utility" (abstract). Peterson et al. reviews the limitations of the xenograft models; see entire document (e.g., page 840, column 2).

Thus, taken collectively, there is a preponderance of factual evidence of record that the showing provided in the supporting disclosure would not enable the skilled artisan to practice the claimed invention without undue experimentation, as required under the provisions of 35 U.S.C.

§ 112, first paragraph.

With regard to Point 1, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). **The MPEP further states that physiological activity can be considered inherently unpredictable.** Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled.

As outlined previously, enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that

teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to methods of treating or prevent cancers through the administration of OmpA (comprising the sequence of SEQ ID NO:2) and a tumor antigen. Said methods encompass both *in vitro* and *in vivo* methods of "treating and preventing" cancers.

Breadth of the claims: The claims are extremely broad in that they encompass literally any type of cancer. It should be noted that all the instant claims read on the *in vivo* treatment and prevention of cancers and infections melanomas in humans.

Guidance of the specification/The existence of working examples:

To use the invention as claimed one must be able to determine what composition comprising OmpA and a tumor antigen would be effective in treating or preventing a given type of cancer or infectious agent by generating or enhancing a cytotoxic T cell response. While the specification provides great detail on the ability of recombinant P40 (OmpA) to stimulate the clonal expansion of CD4 T cells which results in Th1 type immune response (including cytotoxic

T cell responses), the specification is silent on the what compositions comprising OmpA (comprising the sequence of SEQ ID NO:2) would induce the claimed effect. Additionally, the instant claims are drawn to all forms of tumor cells and infectious agents, while the specification has demonstrated only a single melanoma cell line (B16F10) that is susceptible to OmpA (in conjunction with a peptide comprising SEQ ID NO:4) [see Example 5 on pages 27-28]. The specification is silent on what receptor is utilized by OmpA making it difficult to determine if a given tumor cell/infectious agent would be susceptible to OmpA treatment.

State of the art: At the time of applicants' invention the art of using compositions comprising OmpA to treat and/or prevent cancers and infections was underdeveloped.

Predictability of the art and the amount of experimentation necessary:

People of skill in the art require evidence that a benefit can be derived by the therapeutic application of a given substance; however, a survey of the relevant art does not indicate that substances such as those claimed provide such benefit. The instant specification fails to provide significant direction on which OmpA compositions, if any, are capable of eliciting a therapeutic/protective response (tumor cell death) when administered to an immunocompetent subject in need. Moreover, the specification is equally silent on how said OmpA compositions are to be administered to said subject. Jain discloses known barriers to the delivery of drugs into solid tumors (Scientific American Vol. 271 No. 1, pages 58-65, July 1994). Impediments to drug delivery include: (1) Non-uniform blood delivery to all areas of the rumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61) and (3) High liquid

pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1). Consequently, the method of administration would vary depending on the tumor type and location of said tumor. Unfortunately, the specification fails to provide guidance to how a given virus should be administered when treating a given cancer.

The specification teaches how to use recombinant OmpA (rP40) to reduce the viability of a melanoma cell line injected into immunodeficient mice to form xenographs and provides *in vitro* data showing effects of OmpA compositions on the expansion of certain T cell populations. However, the specification does not provide any basis for correlating the *in vitro* results with beneficial effects that could reasonably be expected when said compositions are administered *in vivo* to "treat or prevent" cancers. Lacking either direct evidence for *in vivo* benefit, or a reasonable basis for correlating the *in vitro* and xenograft data as exemplified in the instant specification with *in vivo* benefit. Hence, the specification cannot be said to teach how to use the claimed OmpA compositions as pharmaceuticals without undue experimentation. Moreover, while those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are somewhat useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to *in vivo* efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with

their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro)*. Moreover, Dermer (Bio/Technology, 1994, Vol. 12 page 320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature 'for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Additionally, it should be noted that Example 5 is insufficient to provide enablement for the full breadth of the instant claims. Firstly, the xenographs utilized in Example 5 (on page 27-

28 of the specification), comprise a melanoma derived cell line (B16F10). Secondly, said example utilizes a composition comprising OmpA **and** a peptide comprising SEQ ID NO:4 suggesting the need for an antigen component in the composition. Thirdly, the instant claims are drawn to use of OmpA compositions to treat/prevent all types of cancer and infection by infectious agents whereas Example 5 demonstrates only that one OmpA/peptide combination can reduce the viability of cell-line based xenographs in immunodeficient mice. This cannot be extrapolated to the use of OmpA (either by itself or in conjunction with an antigen) against established tumors in an immunocompetent animal. Gura (Science, Vol. 278, 1997 pages 1041-1042) teach that xenographs are not good models for determining the efficacy of a treatment modality since "xenograft tumors don't behave like naturally occurring tumors in humans" (see column 2). Gura illustrates the lack of correlation between efficacy in xenograft model systems and in vivo efficacy in humans when she states that the use of xenografts led them to discover "compounds that were good mouse drugs rather than good human drugs" (see the bottom of column 2 on page 1041).

Consequently, while being enabling for methods utilizing peptides comprising SEQ ID NO:4 and recombinant P40 (OmpA) to reduce the viability of tumor cell based xenographs in immunodeficient mice, does not reasonably provide enablement for the utilization of "OmpA/antigen" combination to treat or prevent cancer in an immunocompetent animal. The specification does not enable any person of skill in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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ROBERT ZEMAN
PATENT EXAMINER

June 6, 2006